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# Uterine, but not ovarian, female reproductive organ involvement at presentation by diffuse large B-cell lymphoma is associated with poor outcomes and a high frequency of secondary CNS involvement

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## Summary

Involvement of the internal female reproductive organs by diffuse large B-cell lymphoma (DLBCL) is uncommon, and there are sparse data describing the outcomes of such cases. In total, 678 female patients with DLBCL staged with PET/CT and treated with rituximab-containing chemotherapy were identified from databases in Denmark, Great Britain, Australia, and Canada. Overall, 27/678 (4%) had internal reproductive organ involvement: uterus (n=14), ovaries (n=10), or both (n=3). In multivariate analysis, women with uterine DLBCL experienced inferior PFS and OS compared to those without reproductive organ involvement, whereas ovarian DLBCL was not predictive of outcome. Secondary CNS involvement (SCNS) occurred in 7/17 (41%) women with uterine DLBCL (two patients with concomitant ovarian DLBCL) and 0/10 women with ovarian DLBCL without concomitant uterine involvement. In multivariate analysis adjusted for other risk factors for SCNS, uterine involvement by DLBCL remained strongly associated with SCNS (HR 14.13, 95%CI 5.09-39.25,  $P<0.001$ ). Because involvement of the uterus by DLBCL appears to be associated with a high risk of SCNS, those patients should be considered for CNS staging and prophylaxis. However, more studies are needed to determine whether the increased risk of secondary CNS involvement also applies to women with localized reproductive organ DLBCL.

## Keywords

Diffuse large B-cell lymphoma, PET, CNS relapse, gynecologic involvement, uterus involvement

## Introduction

Clinical prognostic scores such as the International Prognostic Index (IPI) and the revised IPI (R-IPI) are widely used to predict the outcome of patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL). (1993, Sehn, *et al* 2007) Enhanced discrimination of low- and high-risk patients was reported with the recently developed National Comprehensive Cancer Network (NCCN) IPI (NCCN-IPI), which refined the categorization of age and LDH into more prognostic subgroups and defined bone marrow, central nervous system (CNS), liver/gastrointestinal tract, or lung involvement as poor-risk features. (Zhou, *et al* 2014) While these risk models predict outcome in the large majority of patients with DLBCL, they do not adequately describe the natural history of specific extranodal presentations of DLBCL. For example, testicular DLBCL has a relapse pattern that frequently involves the CNS and with relapse risk still being present several years after treatment. (Cheah, *et al* 2014, Fonseca, *et al* 2000, Vitolo, *et al* 2011, Zucca, *et al* 2003) Awareness of increased risk of secondary CNS involvement (SCNS) in patients with testicular DLBCL has led to development of treatment protocols, which include CNS prophylaxis first line. (Tilly, *et al* 2015, Vitolo, *et al* 2011) Kidney/adrenal involvement by DLBCL confers similar predilection for SCNS and is one of the six individual risk factors in the recently published CNS-IPI model. (Savage, *et al* 2014, Villa, *et al* 2011)

The outcome and relapse pattern of DLBCL involving the female reproductive organs (uterus and/or ovaries), however, have not been studied in details. In a recent Danish-Canadian study, DLBCL involving the female reproductive organs was associated with very poor outcomes, and a study of 323 Chinese DLBCL patients suggests that an increased frequency of SCNS may partially account for this finding. (Cao, *et al* 2014, El-Galaly, *et al* 2015) To study this issue more systematically, we analyzed the clinical characteristics, outcomes, and relapse pattern of women with internal reproductive organ DLBCL in a large cohort of R-CHOP(-like) treated female patients staged with 18F-fluoro-deoxyglucose-positron emission tomography/computed tomography (FDG PET/CT).

## Methods

### Patients

This is an international retrospective study of female patients with newly diagnosed DLBCL. Patients were identified from lymphoma registries and study databases in Denmark (LYFO), Australia (Peter MacCallum Cancer Centre, Melbourne), Great Britain (Guy's and St. Thomas' Hospital, London), and Canada (British Columbia Cancer Agency, Vancouver). The regional/national lymphoma registries have been described in detail elsewhere.(Gang, *et al* 2012, Sehn, *et al* 2005)

Patients diagnosed between 2001 and 2013 were screened for eligibility, but the surveyed time for each hospital site depended on the local availability of PET/CT and database structure. Patients fulfilling the following criteria were included: i) treatment-naïve DLBCL without CNS and/or intraocular involvement, ii) PET/CT pre-treatment staging, and iii) R-CHOP(-like) front-line therapy. Baseline CNS staging with evaluation of cerebrospinal fluid and brain imaging were performed according to unit policy in place at the time and physician discretion.

Baseline clinicopathologic characteristics and treatment information were retrieved from databases and registries. In case of missing information or if the databases/registries did not routinely capture key information, local investigators reviewed individual medical records. Medical records were reviewed for outcomes and in particular relapse site (SCNS) by local investigators. Female patients (n=192) from Aalborg (2007-2012), Rigshospitalet (2009-2012) and BCCA (2011-2012) were previously included in the analyses of PET/CT detected extranodal DLBCL and validation of clinical risk scores in a recent Danish-Canadian study.(El-Galaly, *et al* 2015) In that study, we found that female reproductive organ involvement was associated with inferior outcomes, but detailed analyses of sites (ovarian and/or uterine), relapse patterns, and outcomes were not presented.(El-Galaly, *et al* 2015)

## **Treatment**

All patients were treated with R-CHOP(-like) first-line therapies. The CHOP-like therapies included R-CEOP (doxorubicin replaced by etoposide) for patients with cardiac contraindications for anthracycline therapy and R-CHOEP (addition of etoposide 100 mg/m<sup>2</sup> for three days with each R-CHOP cycle) for selected high-risk patients in Denmark.(Gang, *et al* 2012)

There were no predetermined indications for CNS prophylaxis, although it was generally considered in patients with high-risk features such as multiple extranodal sites of involvement and involvement of particular extranodal sites such as kidneys/adrenals. The prophylactic strategy, including drug, dose, route, and frequency varied according to local guidelines. Similarly, there were no predetermined guidelines for monitoring development of SCNS in asymptomatic patients in follow-up after completion of primary therapy. However, as a rule, routine surveillance studies did not include brain imaging or other CNS directed investigations.

Radiotherapy was used at the discretion of the attending physician. Some of the commonly accepted indications for radiotherapy included solitary extranodal sites, bulky disease, residual PET activity following immunochemotherapy and combinations with abbreviated immunochemotherapy treatment for patients with stage I-II DLBCL. Data collection was compliant with local/national regulations.

## **Statistical analyses**

Patient demographics and clinical characteristics were summarized using descriptive statistics (percentage for categorical values and median for continuous values). Overall survival (OS) was measured from diagnosis until death from any cause, or censoring. Progression-free survival (PFS) was measured from diagnosis until progression/relapse, death, or censoring. PFS and OS were estimated using the Kaplan-Meier method, and compared using the log-rank test.(Kaplan and Meier 1958) Cumulative incidence curves for SCNS were computed using the competing risk regression method proposed by Fine and Gray.(Fine and Gray 1999) Univariate and multivariate associations between

clinicopathologic features and outcomes were examined using Cox proportional hazards regression models.(Cox 1972) In the multivariate models for PFS and OS, uterine involvement, ovarian involvement, and the individual risk factors of the International Prognostic Index (IPI) were included to adjust for confounding regardless of statistical significance in univariate analyses. (1993) (El-Galaly, *et al* 2015)

## Results

### Patients

A total of 678 female DLBCL patients were included in the present study (Denmark n=469; Great Britain n=74; Australia n=91; Canada n=44). The median age was 65 years (range 17-91). R-CHOP was first line treatment in 93% of the patients, R-CEOP in 1%, and R-CHOEP in 6%. Radiotherapy was given to 32% of the patients and 17% received CNS prophylaxis (3% systemic prophylaxis, 7% intrathecal prophylaxis and 6% both types). With a median follow-up of 44 months (reverse Kaplan-Meier method), the 4-year PFS and OS rates were 71% (95% CI 67-74%) and 77% (95%CI 73-80%), respectively.

Reproductive organ involvement was registered in 27/678 female DLBCL patients (4%, 95%CI 3-6%), of whom 14 had uterine involvement by DLBCL, 10 had ovarian involvement by DLBCL, and three had involvement of both organs. Table 1 shows the clinicopathologic characteristics of female DLBCL patients without reproductive organ involvement versus patients with ovarian involvement by DLBCL or patients with uterine involvement by DLBCL (including the three patients with concomitant ovarian and uterine DLBCL). Overall, female DLBCL patients with reproductive organ involvement had higher number of extranodal disease sites and patients with uterine involvement were more likely to have high-risk R-IPI risk score (Table 1). Kidney/adrenal involvement was associated with ovarian involvement by DLBCL (P=0.006). The proportions of patients receiving CNS prophylaxis and

radiotherapy did not differ for patients with or without reproductive organ involvement, although there was a trend toward more use of systemic prophylaxis among patients with ovarian DLBCL.

### **Outcomes of patients with or without reproductive organ involvement**

There was no difference in PFS ( $P=0.36$ ) or OS ( $P=0.42$ ) in women with reproductive organ involvement between the patients from Aalborg, Copenhagen, and BCCA previously reported and patients from additional centres/other time periods in the current study. Similarly there was no difference in PFS ( $P=0.89$ ) or OS ( $p=0.89$ ) in women without reproductive organ involvement, permitting data pooling for the present analysis. The outcomes of patients with ovarian versus uterine (+/- simultaneous ovarian DLBCL) versus no reproductive organ involvement are shown in Table 2 and corresponding survival curves are shown in Figure 1A and 1B. Patients with uterine involvement by DLBCL had worse 4-yr PFS and OS estimates than female patients without reproductive organ involvement and those with only ovarian involvement by DLBCL. Associations between reproductive organ site and outcomes were explored in univariate and multivariate Cox regression analyses (Table 3). By univariate analyses, all individual IPI risk factors as well as uterine involvement by DLBCL were associated with inferior PFS and OS. By multivariate analyses, uterine involvement remained independently associated with inferior PFS (HR=2.28, 95%CI 1.23-4.22,  $P=0.009$ ) and OS (HR 2.34, 95%CI 1.21-4.52,  $P=0.012$ ). Ovarian DLBCL was not associated with outcome in multivariate analyses.

### **Secondary CNS involvement (SCNS)**

SCNS occurred in 27/678 (4%) women during follow-up. The median time to CNS relapse was 9 months (interquartile range 6-19). Eleven of the 27 (41%) patients had documented systemic progression/relapse at the time of SCNS. SCNS was detected by imaging in 17 patients (biopsied in nine patients), by positive CSF analysis for lymphoma in five patients, and by both imaging and CSF analysis in four patients. One patient had intravitreal relapse documented by ophthalmologic



evaluation and visual disturbances that improved with SCNS treatment. SCNS was diagnosed in 7/27 (26%) women with and 20/651 (3%) women without reproductive organ involvement. Notably, none of the 10 patients with ovarian DLBCL as the only reproductive organ site developed SCNS in contrast to 7/17 patients (41%) with uterine DLBCL (including 2 patients with concomitant ovarian and uterine DLBCL). The 4-year cumulative risk of SCNS was significantly higher for patients with uterine involvement by DLBCL as compared to patients without (Table 2, Figure 1C). By univariate Cox analysis, uterine involvement by DLBCL +/- ovarian involvement was associated with increased risk of SCNS (HR 16.51 95% 6.97-39.12,  $P < 0.001$ ). By multivariate analysis including elevated LDH, kidney/adrenal involvement,  $>1$  extranodal site, and stage III/IV disease, all of which are well established risk factors for SCNS (Boehme, *et al* 2009, van Besien, *et al* 1998, Villa, *et al* 2011, Villa, *et al* 2010), the presence of uterine DLBCL remained associated with increased risk of CNS relapse (HR 14.13, 95%CI 5.09-39.25,  $P < 0.001$ ). Among patients with uterine involvement, 5/7 (71%) with SCNS had CNS-IPI score 4-6 (high-risk) at diagnosis as compared to 2/10 patients (20%) without SCNS ( $P = 0.058$ ). Among patients with uterine involvement by DLBCL, 0/7 with SCNS had stage I-II DLBCL as compared to 3/10 (30%) without SCNS ( $P = 0.23$ ). Kidney/adrenal involvement was registered in 27/678 patients (4%), of whom three (11%) developed SCNS. None of the three patients with concomitant kidney/adrenal and ovarian involvement developed SCNS.

As SCNS was seen with unexpectedly high frequency among patients with uterine involvement by DLBCL, pathology files were reviewed. In 11/17 patients (65%), including four with SCNS, uterine involvement by DLBCL was documented by biopsy (in one case of coinciding ovarian and uterine DLBCL, ovarian biopsy was obtained).

## Discussion

The present study examined the outcomes of female DLBCL patients with reproductive organ involvement. Among the 678 patients analysed in this study, patients with uterine involvement by DLBCL had very poor outcomes, whereas patients with ovarian DLBCL had outcomes similar to other

women. The poor outcomes observed for patients with uterine involvement were at least partially explained by an unexpectedly high frequency of SCNS.

Internal reproductive organ involvement was seen in 4% (95%CI 3-6) of female DLBCL patients in the present study, which is slightly higher than the 2% reported by Cao *et al.* (Cao, *et al* 2014) However, the latter study only included primary uterine DLBCL defined as those patients with stage IE-IIIE disease, which likely explains the higher frequency of reproductive organ involvement in our study as 89% patients with reproductive organ involvement also had advanced stage disease. (Cao, *et al* 2014) Similar to testicular DLBCL and kidney/adrenal involvement, DLBCLs originating from the reproductive organs in females are rare and underscores the importance of large databases to study clinical associations and natural history of these unusual DLBCL presentations. (Cheah, *et al* 2014, Villa, *et al* 2011)

The outcomes of women with reproductive organ involvement in the present study were significantly worse than for women without reproductive organ involvement. With multiple other high-risk features being present in these patients, the specific contribution of reproductive organ involvement to the poor outcomes is difficult to assess. However, presence of uterine DLBCL remained associated with poor PFS and OS independent of the IPI risk factors in multivariate analyses. Cao *et al* evaluated six patients with DLBCL originating primarily from the reproductive organs, including four with uterine involvement and two with ovarian involvement. Despite IPI  $\leq 1$  for all patients, the median PFS was only 27 months in that study. (Cao, *et al* 2014) Mandato *et al* conducted an extensive literature review of 144 patients with uterine involvement by DLBCL from cases/case series and derived a mean OS of 46 months from these data. (Mandato, *et al* 2014) The more favourable outcomes of uterine involvement by DLBCL in that study may be explained by the fact that >80% of the patients had limited stage disease. (Mandato, *et al* 2014) Vang *et al* reported a series of 26 patients with uterine involvement by lymphoma, mostly DLBCL, and treated at the MD Anderson Cancer Centre in the period 1981-1998. (Vang, *et al* 2000) In that study, 10/26 patients had localized disease, 12/26 had advanced stage disease, and in 4/26 staging information was insufficient to determine disease stage. The outcomes of patients with localized and non-localized disease differed widely; the 5-year OS of

patients with localized disease was 83% as compared to only 29% for patients with non-localized disease.(Vang, *et al* 2000) This supports our observation of poor outcomes for patients with advanced stage disease and uterine involvement.

In our study, 7/17 (41%) women with uterine DLBCL experienced SCNS and this was the major determinant of the poor outcomes seen in patients with reproductive organ involvement. Our findings are consistent with the series by Cao *et al* in which 4/6 patients with reproductive organ involvement experienced SCNS (3/4 had uterine involvement).(Cao, *et al* 2014) In the literature review by Mandato *et al*, at least two out of five patients with disease recurrence <6 months after treatment had SCNS.(Mandato, *et al* 2014) Thus, the risk of SCNS among women with uterine involvement by DLBCL appears to be substantial and clinically relevant, although the simultaneous presence of R-IPI high-risk disease is a confounder. However, uterine DLBCL was associated with SCNS after adjustment for other risk factors and the observed cumulative incidence for this group of patients was substantially higher than the 2-year cumulative SCNS risk of 12% reported for CNS-IPI high-risk disease.(Savage, *et al* 2014)

None of the 10 women with ovarian DLBCL as the only site of internal reproductive organ involvement developed SCNS, and involvement of ovaries was not associated with outcomes in multivariate analyses. In two retrospective case series including 13 patients with ovarian lymphoma, mainly limited stage DLBCL, the outcomes were favourable and similarly, no SCNS cases were reported.(Senol, *et al* 2014, Vang, *et al* 2000) In contrast, Yun *et al* reported SCNS in 5/22 women with ovarian DLBCL without baseline CNS involvement, but 4/5 had additional high-risk features for SCNS including IPI $\geq$ 3.(Yun, *et al* 2010) Thus, data on SCNS risk with ovarian DLBCL is conflicting. The explanation for increased risk of SCNS with specific extranodal sites is unclear. From an embryologic standpoint, intermediate mesoderm gives rise to the internal female genital tract as well as other high-risk sites including the testes, kidneys, and adrenal glands.(Sadler 2015)

This study has limitations inherent to its retrospective design. No central pathology review was performed and information regarding cell of origin and the presence of adverse cytogenetic lesions (MYC and BCL2 or BCL6 translocations) was not available in the vast majority of patients. Double hit

DLBCL is associated with an increased risk of SCNS and may have been present in at least some of the patients in our study with poor-risk disease and uterine DLBCL.(Oki, *et al* 2014, Savage, *et al* 2016). Uterine involvement by DLBCL was based on imaging alone in some patients, and it is relevant to question the presence of DLBCL in these lesions. However, the frequency of biopsy verification of uterine involvement (11/17 patients) was high, considering many presented with advanced stage disease with other sites potentially more amenable to diagnostic biopsy. We speculate that unusual presentation of DLBCL at these sites and the need to rule out more common malignancies, particularly endometrial adenocarcinoma, may account for the high rate of histology documentation. In contrast to uterine DLBCL, we did not observe poorer outcomes in female patients with ovarian DLBCL as the only site of reproductive organ involvement. Physiologic FDG-uptake can occur in relation to the ovulatory phase of the menstrual cycle in premenopausal women.(Lerman, *et al* 2004) However, the median age of the 10 patients with ovarian DLBCL as the only reproductive organ involvement was 60 years and only 2/10 were below 50 years. Therefore, misinterpretation of physiological FDG-uptake in the ovaries is unlikely to explain reporting of ovarian DLBCL in most cases.

In conclusion, women with uterine involvement by DLBCL appear to have poor outcomes, largely related to the high risk of SCNS. Staging of the CNS at diagnosis in those patients is reasonable, and CNS prophylaxis should be considered. However, additional studies are needed to confirm whether DLBCL originating from the female reproductive organs carries a significant risk of SCNS, particularly in the absence of other high-risk features.

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TEG, CC, MH and DV designed the research. TEG, MB, CC, and DV planned and/or performed the statistical analysis. TEG, CC, KR, NGM, SB, KJM, SL, SH, KB, SC, JWH, MH, PB, DS, MP, MJ, DV and MC reviewed patient records and/or collected data. All authors interpreted data. All authors wrote the manuscript. All authors critically revised the paper and approved the final version.

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## Tables and Figures

**Table 1: Detailed baseline characteristics and treatment information of female DLBCL patients with or without reproductive organ involvement.**

	Female DLBCL patients (n=678)				
	No reproductive organ involvement (n=651)	Ovarian involvement (n=10)	<i>P</i> <sup>*</sup>	Uterine involvement (n=17)	<i>P</i> <sup>§</sup>
Median age, years (range)	65 (17-91)	60 (33-84)	<0.001	66 (44-82)	<0.001
Ann Arbor stage, n (%)					
• Stage I-II	243 (37)	0	0.02	3 (18)	0.13
• Stage III-IV	408 (63)	10 (100)		14 (82)	
More than one extranodal site, n (%)	154 (24)	6 (60)	0.02	12 (71)	<0.001
Median number of extranodal sites, n (interquartile range)	1 (0-1)	2 (1-3)	<0.001	2 (1-4)	<0.001
Kidney/adrenal involvement, n (%)	24 (4)	3 (30)	0.006	0	1.0
Elevated LDH, n (%) <sup>¥</sup>	335 (52)	7 (70)	0.35	10 (59)	0.63
ECOG performance score >1, n (%) <sup>¥</sup>	103 (16)	2 (20)	0.66	5 (29)	0.17
R-IPI risk group, n (%) <sup>¥</sup>					
• Very good risk (score 0)	71 (11)	0	0.53	0 (0)	0.017
• Good risk (score 1-2)	307 (48)	4 (40)		4 (24)	
• Poor risk (score 3-4-5)	266 (41)	6 (60)		13 (76)	
CNS prophylaxis including intrathecal treatment, n (%)					
• Systemic CNS prophylaxis	62 (10)	3 (30)	0.066	2 (12)	0.67
• Intrathecal	87 (13)	3 (30)	0.14	2 (12)	1.0
Consolidative radiotherapy, n (%)	209 (32)	1 (10)	0.18	5 (29)	1.00

<sup>\*</sup>P-values reflect comparison of female DLBCL patients with ovarian involvement (without simultaneous uterine involvement) versus female patients without internal reproductive organ involvement.

<sup>§</sup>P-values reflect comparison of female DLBCL patients with uterine involvement (+/- ovarian involvement) versus female patients without internal reproductive organ involvement.

<sup>¥</sup>Missing information regarding LDH values (n=6) and ECOG performance (n=1), therefore exact R-IPI was unavailable in seven patients.

**Table 2: Treatment outcome in female DLBCL patients with or without reproductive organ involvement.**

	No reproductive organ involvement (n=651)	Ovarian involvement (n=10)	<i>P</i> *	Uterine involvement (n=17)	<i>P</i> §
4-yr PFS, % (95% CI)	72 (68-76)	70 (33-89)	0.61	26 (8-50)	<0.001
4-yr OS, % (95% CI)	79 (75-82)	69 (30-89)	0.41	33 (12-56)	<0.001
4-yr cumulative CNS relapse rate	4 (2-6)	0	0.58	44 (24-71)	<0.001

\*P-values reflect comparison of female DLBCL patients with ovarian involvement (without simultaneous uterine involvement) versus female patients without internal reproductive organ involvement.

§P-values reflect comparison of female DLBCL patients with uterine involvement (+/- ovarian involvement) versus female patients without internal reproductive organ involvement.

**Table 3: Associations between baseline clinic-pathological features and outcome (PFS and OS) in univariate and multivariate Cox regression analyses. HR=hazard ratio**

	PFS		OS	
	Univariate HR (95%CI, P)	Multivariate HR (95%CI, P)	Univariate HR (95%CI, P)	Multivariate HR (95%CI, P)
Age >60 years	1.97 (1.41-2.76, P<0.001)	1.60 (1.14-2.26, P=0.007)	2.85 (1.86-4.35, P<0.001)	2.38 (1.55-3.66, P<0.001)
ECOG performance >1	2.35 (1.71-3.24, P<0.001)	1.61 (1.16-2.25, P=0.005)	2.74 (1.93-3.90, P<0.001)	1.84 (1.28-2.64, P=0.001)
Elevated LDH	2.87 (2.10-3.93, P<0.001)	2.08 (1.50-2.89, P<0.001)	3.35 (2.32-4.85, P<0.001)	2.46 (1.67-3.63, P<0.001)
Stage III/IV disease	3.29 (2.27-4.76, P<0.001)	2.11 (1.41-3.15, P<0.001)	3.16 (2.07-4.82, P<0.001)	1.79 (1.13-2.84, P=0.013)
>1 extranodal site	2.00 (1.49-2.69, P<0.001)	1.14 (0.82-1.57, P=0.43)	2.13 (1.53-2.97, P<0.001)	1.15 (0.80-1.67, P=0.45)
Uterine DLBCL	3.13 (1.74-5.63, P<0.001)	2.28 (1.23-4.22, P=0.009)	3.57 (1.93-6.60, P<0.001)	2.34 (1.21-4.52, P=0.012)
Ovarian DLBCL	1.72 (0.71-4.18, P=0.23)	0.95 (0.38-2.38, P=0.91)	2.03 (0.83-4.94, P=0.12)	1.12 (0.44-2.87, P=0.81)

## FIGURE LEGENDS

**Figure 1A-C:** Progression-free survival (A) and overall survival (B) for female DLBCL patients with or without internal reproductive organ involvement. Cumulative incidence curves (C) for secondary CNS involvement for female patients with versus without uterine involvement by DLBCL based on Fine and Gray's competing risk model.